American Journal of Medical Genetics 62:42–47 (1996)

Cataracts, Motor System Disorder, Short Stature, Learning Difficulties, and Skeletal Abnormalities: A New Syndrome?

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We present a 4-generation family in which affected individuals have cataracts, a motor neuronopathy with upper motor neuron signs, short stature, developmental delay, and skeletal abnormalities. An additional symptom is weakness during pregnancy which resolves after delivery. The condition is inherited in an autosomal dominant manner. The manifestations and inheritance are not found in any previously described conditions. We consider that this is a new syndrome. © 1996 Wiley-Liss, Inc.

KEY WORDS: cataracts, motor system disorder, autosomal dominant

INTRODUCTION

In this report we describe a 4-generation family with cataracts, a motor neuronopathy with upper motor neuron signs, short stature, and skeletal abnormalities. Other findings in the propositus include persistent vomiting and weight loss and developmental delay. Several relatives have noted weakness during pregnancy, which improved after delivery. We conclude that this combination of findings has not been reported previously.

CLINICAL REPORT

The pedigree of the family is shown in Figure 1. A summary of the clinical findings is provided in Table I.

Patient IV-1

The propositus (Fig. 2) was the first child of healthy, nonconsanguineous Caucasian parents. He was born at 38 weeks of gestation by elective cesarean section performed for cephalopelvic disproportion. Birthweight was 2,285 g (<3rd centile) and head circumference (OFC) was 32.6 cm (3rd–10th centile). There were no significant perinatal problems.

At age 11 weeks, an increase in lower limb tone and symmetrically brisk tendon jerks were noted. At age 2 years, the reflexes were brisk, and crossing of the knee and adductor reflexes were noted. There was no clonus, and the plantar responses were flexor. At age 9 years he was generally weak, with a poor grip and marked muscle weakness of shoulder girdles. Loss of muscle bulk was recorded. He was hypotonic, but his reflexes remained symmetrically brisk, and the plantar responses were flexor.

At age 8 months cataracts were noted and treated by lensectomies. The type and the location of the cataracts were unknown. Results of a congenital viral infection screen, thyroid function tests, and galactose-l-phosphate-uridyl transferase levels were normal.

A skeletal survey performed at a chronological age of 8 months showed a bone age of 3 months. The delay in bone age has been confirmed on several occasions. Other radiological findings include bilateral shallow acetabula with a reduction in the angulation of the femoral heads (Fig. 3), small carpal bones, and shortening of the base of the anterior fossa and basisphenoid.

Feeding difficulties and persistent vomiting were reported in the neonatal period. A barium swallow was normal at age 2 years, but a repeat study at age 8 years showed a small hiatus hernia, and drug therapy was commenced. A Nissen fundoplication was performed at age 11 years. A gastrostomy tube was inserted when this procedure did not result in weight gain.

His psychomotor development was severely delayed. He walked independently from 3-1/2 years, and at the age of 8 years, verbal comprehension was at a 2–3 year-old level.

His height and weight have consistently been below the 3rd centile. His OFC was relatively preserved compared to his height, although the measurements remained below the 3rd centile. He has normal hearing, and there is no retinopathy.

Examination at the age of 13 years showed a thin, weak child with a generalized decrease in muscle bulk. There was weakness of both proximal and distal mus-

Received for publication April 7, 1995; revision received August 14, 1995.

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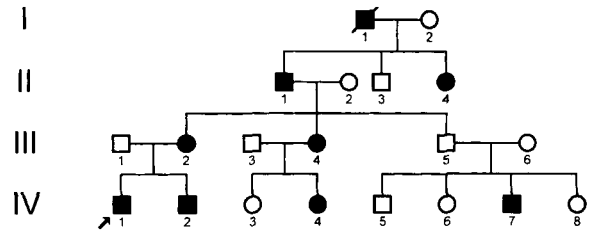

Fig. 1. Family pedigree.

cle groups. The tone was normal. The deep tendon reflexes were normal in the upper limbs, but brisk at the knees. They were absent at the ankles, and the plantar responses were flexor. There was no ataxia. Fasciculations and sensory abnormalities have not been noted. There were no notable minor anomalies.

Results of investigations of thyroid function, thyroid autoantibodies, plasma lactate, plasma ammonia, very long chain fatty acids, plasma phytanic acid, urine organic acids, cerebrospinal fluid (CSF) protein, and CSF lactate were unremarkable. Urine mucopolysaccharides showed an abnormal pattern suggestive of Morquio or GM1 gangliosidosis, but white cell enzymes were normal. Elevated levels of plasma methionine and homocystine were reported on one occasion. The levels were thought to be nondiagnostic, and on repeat testing, normal levels were found. Urine amino acids showed a mild aminoaciduria which was thought not to be diagnostic. At the age of 12 years, plasma creatine kinase was mildly elevated (249 U/L; normal range 70–150 U/L). A magnetic resonance image (MRI) scan of the brain was normal. Cytogenetic analysis has revealed a normal male karyotype on 2 occasions.

A nerve conduction electromyogram (EMG) at age 11 years showed a neurogenic pattern with normal motor nerve conduction velocities, suggestive of axonal degeneration. There were no sensory abnormalities. The compound muscle action potential was very small, perhaps due to the lack of muscle mass.

A muscle biopsy at age 11 years showed atrophic fibers with normal fiber structure, and no abnormal storage or inclusions were seen. There was a slight increase in endomyseal connective tissue, and a considerable amount of perimyseal fat. The appearances were consistent with longstanding denervation and reinnervation.

Patient IV-2

The patient's brother was born at 39 weeks of gestation by cesarean section for cephalopelvic disproportion. Birth weight was 2,700 g (3rd–10th centile).

He was noted to have bilateral cataracts at age 7 months, and was treated with bilateral lensectomies. The type and the location of the cataracts were not recorded. At age 9–18 months, he was thought to show signs of early spasticity with increased tone, but there has been no progression of his neurological signs. Radiological findings at age 5 years showed a reduction of the angulation of the femoral necks with shallow ac-

TABLE I. Clinical Findings in 9 Affected Family Members*

Feature	I-1	II-1	II-4	III-2	III-4	IV-1 proposita	IV-2	IV-4	IV-7
CNS									
Muscle bulk	Not known	Normal	Normal	Normal (↓)	Normal	↓	Normal	Not known	Not known
Tone	Not known	↑	Normal	Normal (↑)	Not known	Normal (↑)	Normal (↑)	Not known	Not known
Power	↓	Normal	→↑	Normal (↓)	Normal (↓)	→↑	Normal	Not known	Not known
Reflexes	Not known	↑	↑	Normal (↑)	Not known	↑	Normal	Not known	Not known
Plantar reflex	Not known	Equivocal	Extensor	Normal (ext.)	Not known	Flexor	Flexor	Not known	Not known
Sensation	Not known	Normal	Normal	Normal	Not known	Normal	Normal	Not known	Not known
Developmental	Not known	–	Not known	–	Not known	+	–	Not known	Not known
Weakness in pregnancy	NA	NA	Not known	+	+	NA	NA	NA	NA
Eyes									
Cataracts	+	–	Not known	–	Not known	+	+	+	+
Age of onset	8 years					8 months	7 months	1 year	3 years
Skeleton									
Short stature	Not known	+ (<3rd)	Not known	+ (<3rd)	+ (3–10th)	+ (<3rd)	+ (<3rd)	Not known	Not known
Dysplastic base of skull	Not known	+	Not known	+	Not known	+	+	Not known	Not known
Dysplastic hips	Not known	–	+	+	Not known	+	+	Not known	Not known
Delayed bone age	Not known	Not known	Not known	+	Not known	+	Not known	Not known	Not known

* The most recent neurological examination findings are recorded, with the findings from previous examinations shown in parentheses.
CNS, central nervous system; ext., extensor; NA, not applicable.

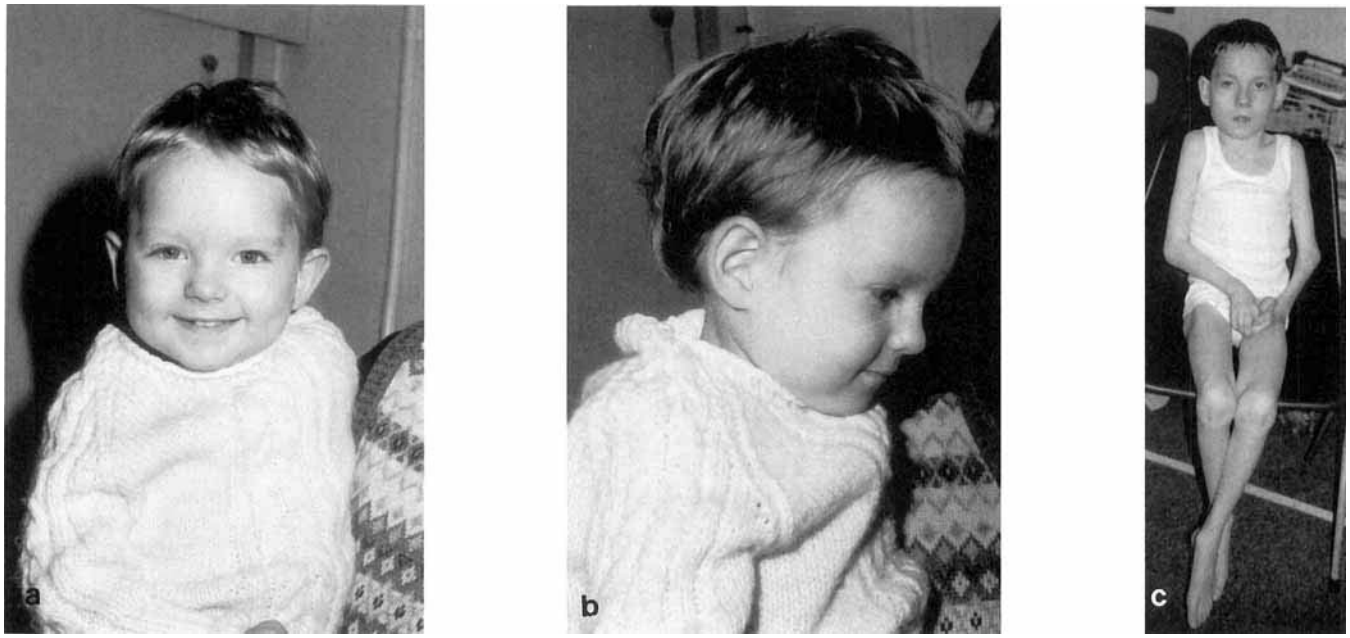

Fig. 2. **a–b:** The propositus at age 3 years. **c:** The propositus at age 12 years.

etabula. A short anterior fossa and basisphenoid were also reported. There were no feeding difficulties, and development was normal.

On examination at the age of 8 years, height and weight were just below the 3rd centile, and there were no minor anomalies. There was no muscle wasting or weakness, and his tone was normal. The reflexes were normal, and his plantar responses were flexor.

Patient III-2

The patient's mother was born after a normal pregnancy weighing 3,400 g (50th centile). She was noted to feed poorly in the first 5 months of life. She was investigated for short stature and failure to thrive at the age of 5 years, but no diagnosis was made. Investigations at that time showed a bone age of 2 years. Other skeletal findings include bilateral hip subluxation, treated by derotation femoral osteotomies at age 7 years, and bilateral plano-valgus foot deformities, surgically corrected at age 15 years. Radiographs have shown a short left femoral neck with a shallow acetabulum, and short 5th digits with bilateral flattening of the heads of the 3rd and 4th metacarpals. Her pituitary fossa was reported to be small, and the base of the anterior cranial fossa was thickened with a short basisphenoid.

An ophthalmological examination at age 32 years showed faint opacities in both lenses that were considered to be normal. Her height was 147.5 cm, and there were no anomalies apart from 5th finger clinodactyly (Fig. 4).

She first developed bilateral weakness and wasting of the small muscles in her hands at 7 months of pregnancy with the propositus. The weakness spread to her arms and legs, and was sufficiently severe to enforce bed rest from 36 weeks of pregnancy. Neurological assessment at 2 months following delivery showed bilateral wasting of the thenar and hypothenar eminences and wasting of the small muscles of the hands with ulnar clawing. There was weakness of the distal muscle groups in the upper limbs, and of the proximal muscle groups in the lower limbs. The tone was increased, and there was nonsustained clonus of the knees and ankles. The abdominal reflexes were present. The tendon reflexes were brisk, and the plantar responses were extensor. There were no fasciculations, and sensory symptoms and signs were absent. Examination of the cranial nerves was unremarkable. Results of routine hematological and biochemical tests were uninforma-

Fig. 3. Radiograph of the pelvis showing shallow acetabula and a reduction in the angulation of the femoral heads in the propositus.

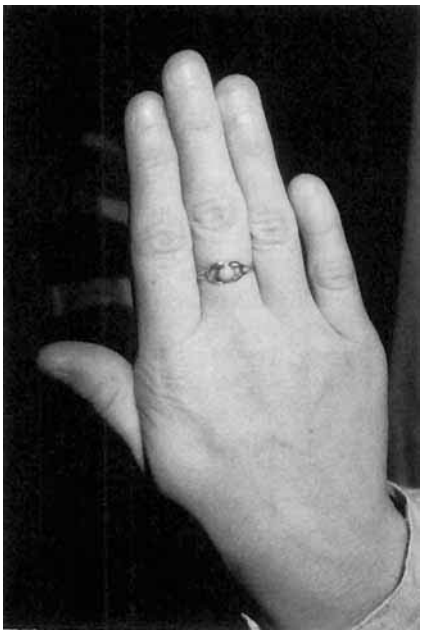

Fig. 4. Hands of the mother of the propositus.

tive, and tests for luetic infections were negative. A cervical myelogram and computed tomographic (CT) scan of the brain were normal.

Neurophysiological studies showed denervation of the small muscles of the left hand, but, in spite of the denervation, there was a marked monosynaptic reflex. Denervation of the left brachioradialis, biceps, and triceps muscles was also seen. The reflexes were very large in amplitude with the exception of the left biceps jerk, which was smaller in amplitude, and had a prolonged latency. There was no evidence of involvement of the peripheral sensory nerve fibers.

The weakness improved one month after delivery, and she symptomatically recovered with no weakness and normal reflexes at 6 months after delivery.

A similar illness was noted during her second pregnancy. She complained of weak legs at 6 months of pregnancy, and required a walking frame before delivery. Examination showed normal tone, mild distal weakness of both arms, and more marked proximal weakness of both legs. The tendon reflexes were symmetrically increased, and the plantar responses were extensor. Fasciculation was observed on one occasion.

Repeat neurophysiological testing showed denervation of the right brachioradialis and the right biceps muscles. All of the upper limb reflexes were large in amplitude, suggesting upper motor neuron pathology. There was severe denervation of right quadriceps muscle. The right knee jerk had a normal latency, but the amplitude was very large. The symptoms improved following delivery, and no diagnosis was made.

Later testing with magnetic brain stimulation gave clear evidence of dysfunction of the corticospinal tract with a raised threshold for activating the motor cortex, and prolongation of the central motor conduction time to the intrinsic hand muscles.

Patient II-1

Individual II-1 reached a final height of 158 cm. Neurological examination at age 60 years documented hypertonia in both upper and lower limbs, and symmetrically increased reflexes. There was no muscular weakness or wasting, and the plantar responses were equivocal. Neurophysiological testing showed normal motor and sensory nerve conduction measurements, and there was no evidence of denervation in the biceps muscle. However, magnetic brain stimulation confirmed involvement of the corticospinal tract, with a raised threshold for activating the motor cortex, and prolongation of the central motor conduction time to the intrinsic hand muscles. An ophthalmological examination did not show lens opacities. Radiography showed a short anterior fossa, but the angulation of the femoral heads in the acetabula was normal.

Patient II-4

Individual II-4 was investigated for right hip pain and difficulty walking at age 37 years. On examination, tone and muscle bulk were normal, but there was a mild, asymmetrical proximal weakness of the upper limb muscles and generalized leg weakness bilaterally. The reflexes were symmetrically brisk, but the ankle jerks were absent. The plantar responses were extensor. Pes cavus and bilateral clawing of the toes were noted. A diagnosis of Friedrich's ataxia was suggested, but neurophysiological testing was not performed.

Patient I-1

Individual I-1 was reported to have had cataracts at age 8 years, and to have had "muscle weakness" and pes cavus later in life.

Patient III-4

Individual III-4 reportedly noted transient weakness in the fingers of both hands during her pregnancies which resolved after delivery. There was no loss of muscle bulk, and her arms and legs remained unaffected. Her final height was 152.5 cm.

Patient IV-4

Individual IV-4 was noted to have bilateral lamellar cataracts before age 2 years.

Patient IV-7

Individual IV-7 had bilateral cataracts, and was treated by lensectomies at age 3 years.

DISCUSSION

In this family, there is a condition comprising cataracts, motor system disorder, short stature, learning difficulties, and skeletal abnormalities including delayed bone age and "dysplastic" hips and base of skull (Table I). The pedigree suggests an autosomal dominant pattern of inheritance. Literature and data base searches have not uncovered a syndrome that can account for these findings.

One of the most prominent aspects of the condition in this family is that of a motor neuronopathy with upper motor neuron dysfunction. The weakness in the pa-

tient's mother was initially diagnosed as a benign form of spinal muscular atrophy (SMA) aggravated by pregnancy, although this diagnosis was discarded when her symptoms resolved. Hereditary SMA is characterized by weakness and wasting of the limb muscles and denervation caused by degeneration of the anterior horn cells [Gilliam and Brzustowicz, 1993]. Childhood SMA can be rarely inherited as an autosomal dominant condition [Emery, 1971; Pearn 1980], and in at least one family, the onset of muscular symptoms was found to occur after pregnancy in an affected individual [Rietschel et al., 1992]. However, the presenting neurological signs in the propositus (hypertonia and hyperreflexia) are inconsistent with SMA, and the upper motor neuron pathology seen on neurophysiological testing does not support this diagnosis. To our knowledge, SMA has not been described in association with cataracts or skeletal abnormalities.

Weakness and cataracts are common presenting complaints in myotonic dystrophy [Harper, 1979]. However, molecular testing with standard laboratory procedures in the propositus and his mother has not found an abnormal DNA expansion in the chromosome region associated with myotonic dystrophy.

Progressive muscular weakness with mildly elevated creatine phosphokinase levels, short stature, skeletal abnormalities, and delayed development can also be found in Marinesco-Sjögren syndrome [Superneau et al., 1987; Komiyama et al., 1989]. In this family, the autosomal dominant pattern of inheritance and the absence of cerebellar atrophy exclude the diagnosis of Marinesco-Sjögren syndrome.

Cataracts and musculoskeletal abnormalities are also common manifestations of Stickler syndrome [Stickler et al., 1965; Liberfarb et al., 1981]. The absence of sensorineural deafness, cleft palate, characteristic face, and spondyloepiphyseal dysplasia in this family makes the diagnosis of Stickler syndrome unlikely [Temple, 1989].

The association of mental retardation, short stature, ocular abnormalities, and neurological findings also raises the possibility of mitochondrial or peroxisomal disorders. However, the pattern of inheritance, and normal levels of CSF lactate, very long chain fatty acids, and phytanic acid make these possibilities less likely.

Another interesting manifestation in this family is weakness during pregnancy. Mononeuropathies, e.g., compression of the median nerve causing carpal tunnel syndrome, have long been described in pregnancy, and are thought to be caused by unsuspected trauma, weight gain, and fluid retention [Massey and Cefalo, 1979; Hopkins, 1989]. Pregnancy has also been reported to exacerbate mitochondrial myopathies [Berkowitz et al., 1990]. Polyneuropathies, such as gestational and recurring polyneuritis, have also been documented in pregnant women [Calderón-González et al., 1970; Massey and Cefalo, 1979]. However, the weakness in male relatives makes such diagnoses less satisfactory explanations for the symptoms suffered by the patient's mother during her pregnancies.

Finally, a further characteristic in this family is the anticipation of symptoms. Anticipation can be genetically defined as increasing clinical involvement and/or earlier onset of symptoms in successive generations [Riggins et al., 1992]. In this family, the propositus was noted to have neurological signs in his first year of life, whereas his mother's symptoms were first apparent at age 22 years. In the preceding generation, individual II-4 presented with weak legs at age 37 years.

Anticipation is a characteristic of single gene disorders caused by an abnormal expansion of trinucleotide repeats [Abbott and Chambers, 1994]. Examples of such conditions include Kennedy disease [La Spada et al., 1991], myotonic dystrophy [Harley et al., 1992], Huntington disease [The Huntington's Disease Collaborative Research Group, 1993], denatorubral-pallidoluysian atrophy [Koide et al., 1994; Nagafuchi et al., 1994], and Machado-Joseph disease [Kawaguchi et al., 1994]. All of these conditions have a neurological component, and it has been thought that the expansion of unstable trinucleotide repeats might represent the commonest genetic mechanism for dominantly inherited neurodegenerative disorders [Miwa, 1994]. Such a mechanism may be responsible for the anticipation demonstrated by this family.

In summary, we report a family with congenital cataracts, motor system disorder with upper motor neuron signs, short stature, learning difficulties, and skeletal abnormalities with an autosomal dominant pattern of inheritance. We conclude that this syndrome has not been described previously. The pedigree shows anticipation, and we hypothesize that an unstable trinucleotide repeat may be responsible for the condition.

ACKNOWLEDGMENTS

We are grateful to Dr. Ronald Smith for referring the family for investigation, and to Professor Anthony Bron and Dr. Hung Cheng for performing ophthalmological examinations on the family.

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